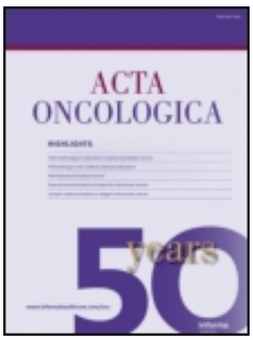

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RENAL TUMORS WITH PSEUDOHERMAPHRODITISM AND GLOMERULAR DISEASE

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From 1972 through 1991, 404 patients with renal tumor (Wilms' tumor and clear cell sarcoma) were seen at the Pediatric Oncology Unit of Hacettepe Children's Hospital. The genital abnormalities and renal diseases in these patients were evaluated retrospectively. Eight patients with renal tumor had genital abnormality and/or renal disease of various types and degrees. One of these patients had a clear cell sarcoma while all the others had Wilms' tumor. Two patients had all components of the Drash syndrome. Two patients with Wilms' tumor had genital abnormality and mild proteinuria. Another two patients had only Wilms' tumor and renal disease. Two patients had only renal tumor and genital abnormality of whom one was the patient with clear cell sarcoma.

Wilms' tumor, male pseudohermaphroditism and glomerulopathy is a well-known triad (1–6). Denys et al. (4) first described Wilms' tumor and glomerulotubular disease in a male pseudohermaphrodite in 1967 and Drash et al. (5) suggested this triad as a syndrome in 1970. The triad has been named Drąsh syndrome or Denys-Drash syndrome (1, 5, 7, 8). Recently, patients with two components of this syndrome were described and named partial Drash syndrome (1, 9–15).

In the present survey, 8 cases of renal tumors in childhood, combined with genital abnormality and/or renal disease, are reported. One of them had clear cell sarcoma and pseudohermaphroditism, a combination that does not seem to have been reported previously.

Material and Methods

From January 1972 through December 1991, 404 patients with renal tumor (Wilms' tumor and clear cell sarcoma) were diagnosed, treated, and followed up at the Pediatric Oncology Unit of Hecettepe Children's Hospital. The records of these patients were retrospectively evaluated concerning genital abnormality and renal disease. The clinical and operative findings were used for detecting genital abnormalities which included genital ambiguity; other genital abnormalities were not included. Renal disease was evaluated on the basis of clinical findings, urine analysis, and biochemical findings. Biopsy of the contralateral kidney or of the non-tumorous part of the ipsilaterial kidney was performed in two patients only.

Results

Eight (2%) out of the 404 patients with renal tumor had genital abnormality and/or renal disorder. Clinical and laboratory findings in these patients are shown in the Table. One patient (case 6) had a clear cell sarcoma and all the others had Wilms' tumor. Four out of these 8 cases had nephrotic syndrome and three of them (cases 4, 5, 8) died early from renal failure. Open renal biopsy from the contralateral kidney was performed in case 4 and from a non-tumorous part of the ipsilateral kidney in case 8; histology showed in both cases focal sclerosing glomerulonephritis.

Case 6 was a 3 1/2-year-old boy, operated on in another center with left-side nephrectomy for a clear cell sarcoma. Lung metastases were detected 7.5 months later and he was referred to our hospital. Physical examination revealed an 8 × 8 cm mass in the left upper quadrant of the abdo-

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Table

*Clinical and laboratory features of eight patients with renal tumor, genital abnormality and glomerulopathy**

No.	Age (y) /sex	Chromosome analysis	Genital abnormality	Renal disease								End results	(months)
				P	HU	CU	HT	BA	Nephrotic syndrome	Biopsy	Renal failure		
1	3/M	46 XY	Ambiguous genitalia right abdominal testis	+	+	−	+	−	−	−	−	Died	(2.5)
2	4/M	46 XY aniridia, cataract, lens subluxation, MMR	Ambiguous genitalia right undescended testis	+	−	+	−	+	?	−	−	Lost to follow-up	(96)
3	2/M	BS(−)	Ambiguous genitalia bilateral crypthorchidism, no gonads in laparotomy	−	−	−	−	−	−	−	−	Complete remission	(120)
4	4/F	ND	No abnormalities	+	−	−	−	+	+	FGS	+	Died, RF	(7)
5	$1\frac{1}{2}$/F	BS(+)	Ambiguous genitalia	+	−	−	−	+	+	−	+	Died, RF	(4)
6	$3\frac{1}{3}$/M	ND	Ambiguous genitalia	−	−	−	−	−	−	−	−	Lost to follow-up	(25)
7	$1\frac{1}{2}$/M	46 XY	Ambiguous genitalia no gonad externally	+	+	−	−	+	+	−	−	Complete remission	(18)
8	2/F	ND	No abnormalities	+	+	+	+	+	+	FGS	+	Died, RF	(2)

ND: Not done, P: Proteinuria, HU: Hematuria, CU: Cylindruria, HT: Hypertension, BA: Biochemical abnormalities, BS: Buccal smear FGS: Focal glomerulosclerosis; *: Case 6 had clear cell sarcoma. Case 2 had bilateral Wilms' tumor. All the other patients had unilateral Wilms' tumor. MMR: Mental motor retardation, RF: Renal failure

men, which was also visualized by ultrasonography. Chest x-rays showed metastases in the lower part of the left lung. He had ambiguous genitalia including penoscrotal hypospadias, bifid scrotum, and severe chordee with palpable gonads. Other system findings were normal. The histopathological slides were reevaluated and the diagnosis was confirmed. Chemotherapy and radiotherapy were given. He was lost to follow-up but known to have progressive tumor disease after 25 months.

Nephrectomy with tumor excision was done at the time of diagnosis in all the patients. Systemic chemotherapy, including vincristine and actinomycin-D, were given to all patients. Doxorubicin and cyclophosphamide were added to the treatment in case 6. Radiotherapy was given to all patients except case 8, who showed rapid progression and died early.

Discussion

The triad pseudohermaphroditism (PH), nephron disorder, and Wilms' tumor constitutes the complete Drash syndrome while patients with two components of this triad are termed as partial Drash syndrome (9–15). The missing component of the syndrome may not be recognized or not have had time enough to become manifest. Patients who developed the third component later on have been reported (1, 9–15). For this reason patients with partial Drash syndrome should be carefully monitored for the third component and ultrasonography and MRI have been advised for this monitoring (11–13, 16). Patients with gonadal dysgenesis (male PH) should undergo renal ultrasound and the presence of an abnormal renal cortex considered as a risk factor for the development of Wilms' tumor (12, 13). In two of our cases ambiguous genitalia were detected before the diagnosis of Wilms' tumor (cases 2 and 5). The interval was long in case 2 but very short in case 5.

Concerning etiology it has been suggested that there is a genetic or teratogenic defect in the urogenital ridge, which is the embryonic precursor of kidneys and gonads (1, 9, 11, 15, 17). Mutations of the tumor suppressor gene for Wilms' tumor (WT1) may contribute to the abnormal genital development and hereditary Wilms' tumor (18). It has been shown that the WT1 gene is expressed in kidneys and gonadal ridge in developing gonads (18). Intralobar nephrogenic rest, which is a precursor lesion of Wilms' tumor, is sometimes associated with aniridia and Drash syndrome (10, 19). We could not show nephrogenic rests in our cases. One of our cases has clear cell sarcoma (case 6) which suggests that also this type of tumor can be associated with PH. To our knowledge this association has not been reported previously.

Wilms' tumor can be associated with a variety of congenital abnormalities including horseshoe kidney, ectopic

kidney, aplastic or hypoplastic kidney, duplication of the upper urinary tract, hypospadia, crypthorchism, and intersexuality (9, 20–22). One variant of incomplete Drash syndrome, including renal disease and XY gonadal dysgenesis with streak gonads and frequent gonadoblastoma without Wilms' tumor, is known as Frasier syndrome (23). One of our cases (case 2) with Wilms' tumor had multiple congenital anomalies including bilateral aniridia, congenital cataract, lens subluxation, and male PH.

The Drash syndrome was first described in male PH. However, a patient reported by Eddy & Mauer (1) had a left ovotestis and a right dysgenetic gonad. In their literature review, the external genitalia was ambiguous in 77% of 22 patients and 5 of the 22 patients were phenotypically normal females (1). Most of the cases were 46 XY but a mosaic case with XX/XY caryotype has been reported (4). Habib et al. (24) reported a patient with normal female external genitalia and caryotype 46 XX. It has been proposed that the definition of Drash syndrome should be expanded to include all cases in which Wilms' tumor and glomerulopathy are associated with any kind of abnormal gonadal differentiation, not only PH (25, 26). Our series includes three female patients and supports the suggested expansion of the Drash syndrome definition.

Nephropathy may be associated with male PH only or Wilms' tumor only, or both these conditions (24, 26–33). Important features of the nephropathy are early onset and rapid progression to renal failure (24). It is resistant to steroids (26). It is believed that the glomerulopathy in Drash syndrome resembles the diffuse glomerulosclerosis described in congenital and infantile nephrotic syndrome (24, 26–28). It has been proposed that immunological mechanisms and tumoral antigens are responsible for the renal pathology. However, nephropathy can also be seen in male PH without Wilms' tumor. The renal histology must be evaluated in a non-tumorous part of the kidneys. Four patients in our series had nephrotic syndrome. Three of them died early from renal failure. To date there have been no reported cases of familial Drash syndrome (10). Interestingly, the brother of case 7 had a glomerular disease but no other signs of partial or complete Drash syndrome.

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